IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

In re the Application of
Barbara A. Rincavage

Group Art Unit: 3600

Application No. 10086253

Examiner: RINES, Robert D.

Filed: 01MAR2002

For: SYSTEM AND METHOD FOR FILLING MEDICAL PRESCRIPTIONS

REPLY BRIEF

For Appellants:

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STATUS OF CLAIMS

Claims 21 to 40 are pending, stand rejected and are on appeal. Claim 21 is an independent method claim and claims 22 to 30 from claim 21. Claim 31 is an independent system claim and claims 32 to 39 depend from claim 31.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues on appeal are (i) whether the subject matter of claims 21 to 22, 27 to 32 and 37 to 40 would have been obvious under 35 U.S.C. 103(a) over Denny Publication 20040107117 dated June 3, 2004, filed November 25, 2003 ("Denny") and Borsand et al. Publication 20030074225 dated April 17, 2003 ("Borsand") and whether the subject matter of claims 23 to 26 and 33 to 36 would have been obvious under 35 U.S.C. 103(a) over Denny, Borsand and Keresman III, et al. Publication 20010047281 ("Keresman"). This Reply Brief is in response to the January 18, 2011 Examiner's Answer in the above-identified appeal.

ARGUMENT

Claims 21 to 40 are pending, stand rejected and are on appeal.

1. THE REFERENCES DO NOT ESTABLISH OBVIOUSNESS OF THE CLAIMED PHARMACIST DISCRETION INVENTION

On appeal are Appellants' claims to a method and system characterized by a processing center that accepts filled prescription information through a network from a pharmacist in fulfillment of physician prescribed information. But, according to the invention, the pharmacist "filled prescription" information can differ in at least one respect from medication brand or dosage of the prescribed prescription information."

In 2002, known systems permitted a pharmacist to confirm that a prescription was filled or not (Denny) or a pharmacist could telephone a provider to obtain a system certification to fill a varied prescription (Borsand [0121]). Hereinafter, these prior art systems are referred to as "non-discretionary yes/no" systems meaning that a pharmacist has no discretion to report other than a "yes/no" response to a provider prescribed or later "certified" prescription.

Appellants in 2002, noting the increasing cost of health care including pharmaceuticals and appreciating the increasing need for less costly drugs and streamlined mechanisms to substitute same efficacy but less costly medication, foresaw a need for a system to admit of a reasonable pharmacist discretion to streamline medication delivery and decrease costs. Appellants respectfully request the Board to take judicial or administrative notice that today, generic drugs are commonly substituted for prescribed proprietarily-identified drugs and often equivalent but different dosages are provided by pharmacists (with appropriate cautionary advice) in fulfillment of prescriptions. Indeed, in some legal jurisdictions, such changes according to pharmacist discretion are specifically approved by law.

Consequently, Appellants filed the presently claimed "pharmacist fulfillment discretion" invention. The invention is defined by method claims 21 to 30 that recite "entering [a] filled and different medication brand or dosage into [a] processing center in fulfillment of [a] prescribed

prescription" (the new "pharmacist discretion" method recitation) and by system claims 31 to 40 that recite a processing center that "accepts filled prescription information through the network from the pharmacist in fulfillment of the prescribed information but that differs in at least one respect from medication brand or dosage of the prescribed prescription information" (the new pharmacist discretion" system recitation).

The Examiner's Answer continues the rejection of claims 21 to 22, 27 to 30, 31 to 32 and 37 to 40 under 35 U.S.C. 103(a) over Denny Publication 20040107117 dated June 3, 2004, filed November 25, 2003 ("Denny") and Borsand et al. Publication 20030074225 dated April 17, 2003 ("Borsand") and the rejection of claims 23 to 26 and 33 to 36 under 35 U.S.C. 103(a) over Denny, Borsand and Keresman III, et al. Publication 20010047281 ("Keresman").

Appellants' Appeal Brief points out that during patent examination, the PTO bears an initial burden of presenting a *prima facie* case of unpatentability. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); *In re Piasecki*, 745 F.2d 1468, 1472, 223 USPQ 785, 788 (Fed. Cir. 1984). To make out a *prima facie* case of obviousness, the PTO must show in the references (by column and line) the teaching that purportedly renders the invention obvious. See *In re Rijckaert*, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). If the PTO cannot point to express statements or implied suggestions of the claimed method or system invention in Borsand or Denny (the references applied to independent claims 21 and 31) then the rejections must be withdrawn. *See In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

Appellants' position is that the cited references, combined in any manner, do not teach or suggest, i.e., do not make out a *pram facie* case of obviousness of a pharmacist "entering [a] filled and different medication brand or dosage into [a] processing center in fulfillment of [a] prescribed prescription..." (pharmacist discretion method) and do not teach or suggest a processing center that "accepts filled prescription information through the network from the pharmacist in fulfillment of the prescribed information but that differs in at least one respect from

medication brand or dosage of the prescribed prescription information" (pharmacist discretion system).

Appellants' non-obviousness case is argued extensively in the Appeal Brief. The Examiner's Answer does not relevantly respond. The Examiner's Answer fails to point to any relevant teaching or suggestion in Denny, Borsand or Keresman that teaches or suggests the claims 21 to 30 recitation of "entering [a] filled and different medication brand or dosage into [a] processing center in fulfillment of [a] prescribed prescription" (pharmacist discretion method) or the claims 31 to 40 processing center that "accepts filled prescription information through the network from the pharmacist in fulfillment of the prescribed information but that differs in at least one respect from medication brand or dosage of the prescribed prescription information" (pharmacist discretion system). The Examiner's Answer substantially reiterates the same arguments of the final rejection without responding in any relevant respect the Appeal Brief *prima facie* arguments. The rejections of claims 31 to 32 and 37 to 40 under 35 U.S.C. 103(a) over Denny and Borsand and claims 33 to 36 over Denny, Borsand and Keresman must be overturned.

2. THE PATENT OFFICE IMPROPERLY MISCHARACTERIZES THE REFERENCE TEACHINGS

The Examiner's Answer raises further questions of mischaracterizations of teachings of the references. *See In re Chapman*, 595 F.3d 1330 (Fed. Cir. 2010) that require overturning the rejections.

With respect to the Denny teaching, at page 4 to page 5, the Examiner's Answer states "...Denny discloses a prescription fulfillment method, comprising... filling the prescription by the pharmacist... wherein the filled prescription is different from the retrieved prescription in respect of at least one of medical brand and dosage; entering the filled prescription into the processing center in fulfillment of the prescribed prescription...." Notably, the page 4 to page 5 Examiner's Answer refers to numerous Denny paragraphs as purported support for the Answer's arguments. Notably, the Answer does not connect any particular reference paragraph

to the relevant "filled prescription is different from the retrieved prescription in respect of at least one of medical brand and dosage" argument.

Appellants have already responded to the Denny arguments of the Examiner's Answer. The Appellant's Appeal Brief reviews the Denny cited paragraphs by paragraph to show that Denny does not teach a pharmacist "entering a filled and different prescription into a processing system." The Examiner's Answer argument or inference that Denny in any way teaches or suggests "the filled prescription is different from the retrieved prescription in respect of at least one of medical brand and dosage" is a prohibited *In re Chapman* mischaracterization of a reference teaching.

In *Chapman,* the Patent Office mischaracterized a prior art "Gonzalez" reference as teaching (1) a particular polymer linkage between light and heavy polymer chains to form a divalent antibody. But in fact, the Gonzalez teaching was of a polymer attached to *either* a light or to a heavy chain. Additionally, (2) the Patent Office mischaracterized Gonzalez as listing a choice of three possible fragments to form an antibody, one of which was the claimed fragment. But in fact, the Gonzalez list included six different possible fragments (again including one that was the Chapman claimed fragment). The Patent Office argued that the mischaracterization errors were harmless. At page 16 of the attached courtesy *Chapman* copy, the Fed. Circuit noted that in view of (1) the Patent Office mistake as to whether "Gonzalez teaches the use of a polymer to link the light and heavy chains in an F(ab')n fragment... Chapman's use of a polymer to link together two F(ab') fragments may be less likely to be obvious" and (2) the Patent Office mistake as to "the full scope of antibody fragments disclosed in Gonzalez," then any ultimate conclusion on selecting one from the list (to produce Chapman's invention) is unclear with respect to obviousness.

Also, the Fed. Circuit disagreed with a Patent Office argument that the errors were harmless:

> Because we cannot say with confidence that the Board would have reached the same conclusion in the absence of these errors, we are persuaded they are indeed

> harmful. *See Kotteakos v. United States*, 328 U.S. 750, 765 (1946) ("[I]f one cannot say, with fair assurance, . . . that the judgment was not substantially swayed by the error, it is impossible to conclude that substantial rights were not affected." This is not a situation where "an agency's path, though convoluted, can be discerned"....)

Chapman attached copy, page16

The Fed. Circuit overturned the Board rejections and sent the case back to the Board for further consideration.

At page 16, line 6, the Examiner's Answer states "... Denny provides for the pharmacist inputting information representative or indicative of a prescription to be filled (Denny; paragraph [0035])." The Examiner's Answer statement is a misleading truncated statement of the [0035] teaching. The [0035] teaching in its entirety is:

> The pharmacy system 16 includes an input device 70, an output device 72, a central processing unit (CPU) 74, a printer 76, and the communication channel 20. The users of the pharmacy system 16, such as pharmacists, pharmacists' assistants, and administrative personnel associated with the pharmacy, can input information representative or indicative of a prescription to be filled into the pharmacy system 16 via the input device 70 to retrieve the retrieval information discussed above, and, in some instances when authorization is obtained by a physician, to input the prescription information.

First, the Denny pharmacy system 16 is a "home base" system that is independent from a "processing center" (the host system 12) except to receive a prescription and to transmit the yes/no response. Otherwise, the pharmacy system 16 is a home system for storing the pharmacist's prescription to be filled according to information received from the prescriber. The information transmitted to the central process unit 74 is the "non-discretionary yes/no" information of fulfillment that is described throughout Denny. The [0035] passage has no hint or suggestion of the claimed pharmacist discretion method or system. To any extent that the Patent Office cites paragraph [0035] as teaching of the claimed invention; the cite is a mischaracterization of the Denny teaching requiring that the rejections be overturned in accord with *In re Chapman, supra.*

Peculiarly after pages of mischaracterizing intimation that Denny teaches the claimed pharmacist discretion method and system, the Examiner's Answer page 5, acknowledges that "Denny fails to "specifically" indicate that the pharmacist enters filled prescription data that includes pharmaceutical type, quantity, cost or other information" and fails to indicate "wherein the filled prescription is different from the retrieved prescription in respect of at least one of medical brand and dosage...." Indeed, Denny does not teach or suggest in any manner ("specifically" or otherwise) a prescription fulfillment method or system that would admit of the pharmacist discretion.

As to Borsand, the Examiner's Answer page 5 to 6, contends "...it is well known in the prescription fulfillment art for the pharmacist to record or enter into a database, information regarding the specifics of a filled prescription including cost, drug type, and quantity administered to the patient." The Examiner's Answer cites no Borsand disclosure to support this statement. To any extent the contention of the Examiner's Answer is intended to imply the claimed pharmacist discretion, the contention is a mischaracterization of the Borsand teaching.

Again at pages 7 to 8, the Examiner's Answer argues:

> However, as is evidenced by Borsand et al., it is well known in the prescription fulfillment art for the pharmacist to record or enter into a database, information regarding the specifics of a filled prescription including cost, drug type, and quantity administered to the patient. Accordingly, Borsand et al. teach a method wherein said filled prescription data includes information for said presented pharmaceutical type and said presented quantity and "wherein the filled prescription is different from the retrieved prescription in respect of at least one or medical brand and dosage..." (Borsand et al.; paragraphs [0005] [0040] [0056] [0064] [0086] [0118] *see electronic representation of filled prescription).

Appellants have searched Borsand for the quoted "wherein the filled prescription is different from the retrieved prescription in respect of at least one or medical brand and dosage..." text material. The quoted text material does not appear. Appellants have reviewed Borsand paragraphs [0005], [0040], [0056], [0064], [0086] and [0118] for any teaching or suggestion of the claimed pharmacist discretion method or system. No such teaching or suggestion appears. To any extent that the Patent Office cites paragraphs [0005] [0040] [0056] [0064] [0086] [0118]

or in the "electronic representation" as purported teaching of the claimed invention, the cites are a mischaracterization of the Denny teaching. *In re Chapman* requires that the rejections be overturned.

In paragraph [0040], Borsand discloses that "the provider 30 may receive a quick *phone call* from a pharmacy 40 after the provider 30 has issued a prescription 28 to confirm a prescription 28" (emphasis added). The paragraph [0040] Fig. 1 description teaches away from the current invention by specifying the phone call response. *See W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied.* 469 U.S. 851 (1984). A finding that a reference teaches away can preclude a finding that the reference renders a claim obvious. *See DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) ("An inference of non-obviousness is especially strong where the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements."). If Borsand was intended to teach a central processing system-exercised pharmacist discretion, then why require telephonic confirmation with the prescriber?. The paragraph [0040] only describes an old system prior to Appellants' invention of the claimed pharmacist discretion method and system.

The Examiner's Answer mischaracterizes purported relevant teachings of the Denny and Borsand references. *In re Chapman* requires overturning of the 35 U.S.C. §103(a) rejections of claims 21 to 40.

3. DENNY IS NOT PRIOR ART

The Denny Publication 20040107117 reference is a publication that was published on June 3, 2004, filed November 25, 2003. The current application was filed on March 1, 2002.

Prior art for the purpose of 35 U.S.C. §103 (a) is defined by 35 U.S.C. §102. While Denny 20040107117 may be based on prior documents, these documents have not been made of

record and are not part of this case to confirm any 35 U.S.C. §102 prior art teaching.1

35 U.S.C. §102 does not admit of a subsequently filed and published document as prior art and all rejections must be overturned.

4. CONCLUSION

The pharmacist discretion capability provided by the claimed invention is an important aspect of current day cost control preferences for generics in place of brand name pharmaceuticals. Indeed in some instances, the pharmacist substitution discretion is mandated by law. It is a processing center function that was not available or otherwise known on the March 1, 2002 filing date of this invention. The claimed method and processing center admit of a pharmacist filling a prescription with a generic rather than a prescribed name brand or with a dosage that is equivalent but different from prescribed dosage, e.g. 20 pills at half strength for 10 prescribed pills at full strength).

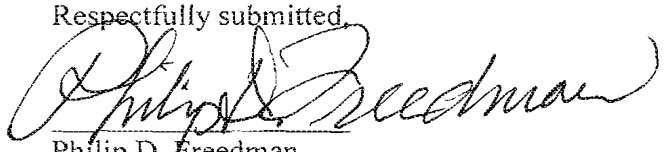
The cited references do not make out a *prima facie* case of obviousness of the claimed pharmacist discretion invention. *In re Chapman* mischaracterizations of the reference teachings require overturning the rejections.

1 For the same reasons, subsequently published Borsand 20030074225, April 17, 2003 is not prior art.

For these reasons. the rejections of claims 21 to 22, 27 to 30, 31 to 32 and 37 to 40 under 35 U.S.C. 103(a) over Denny and Borsand and the rejection s of claims 23 to 26 and 33 to 36 under 35 U.S.C. 103(a) over Denny, Borsand and Keresman should be overturned

Appellant respectfully requests this Honorable Board to overturn the rejections of claims 21 to 40.

Respectfully submitted,



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United States Court of Appeals for the Federal Circuit

2009-1270
(Serial No. 09/719,045)

IN RE ANDREW P. CHAPMAN and DAVID J. KING

Doreen Yatko Trujillo, Cozen O'Connor, P.C., of Philadelphia, Pennsylvania, argued for appellants.

Frances M. Lynch, Associate Solicitor, Office of the Solicitor, United States Patent and Trademark Office, of Alexandria, Virginia, argued for the Director of the United States Patent and Trademark Office. With her on the brief were Raymond T. Chen, Solicitor, and Janet A. Gongola, Associate Solicitor.

Appealed from: United States Patent and Trademark Office
Board of Patent Appeals and Interferences

United States Court of Appeals for the Federal Circuit

2009-1270
(Serial No. 09/719,045)

IN RE ANDREW P. CHAPMAN and DAVID J. KING

Appeal from the United States Patent and Trademark Office, Board of Patent Appeals and Interferences.

DECIDED: February 24, 2010

Before GAJARSA, CLEVENGER, and DYK, Circuit Judges.

DYK, Circuit Judge.

Andrew Paul Chapman and David John King (collectively, "Chapman") appeal from a final decision of the United States Patent and Trademark Office, Board of Patent Appeals and Interferences ("Board"). The Board found claims 1-10 and 12-15 of Chapman's Application Serial No. 09/719,045 unpatentable as obvious. Ex Parte Chapman, No. 2008-0454 (B.P.A.I. May 27, 2008) ("Initial Decision"); (B.P.A.I. Dec. 11, 2008) ("Final Decision"). For the reasons set forth below, we vacate and remand for further proceedings.

BACKGROUND

The technology in this appeal concerns divalent antibody fragments. Antibodies are proteins made of amino acids and bind to antigens to inactivate them as a part of an

immune response. The basic functional units of antibodies are "Y"-shaped and have two identical light chains and two identical heavy chains.

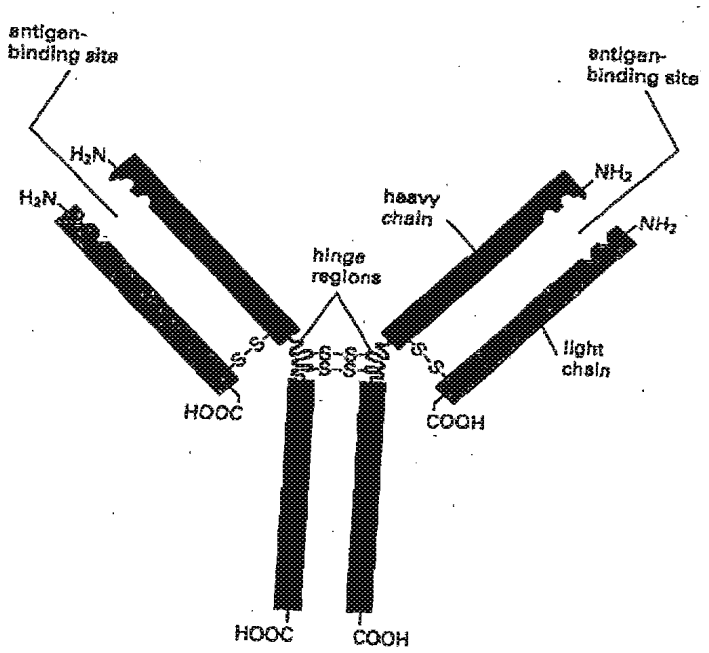

Figure 1.

Appellee's Br. 1-Reverse. As denoted above, each arm of the Y-shape is formed by one light chain and one heavy chain. The two chains are linked by a chemical bond known as a disulphide bridge. The two "arms" of the Y-shape are also linked by disulphide bridges. Disulphide bridges (denoted above as S-S) are formed by a covalent bond between two sulphur atoms from the thiol (-SH) groups in the amino acid cysteine on each chain. At the upper end of each branch of the "Y" are the variable regions of the antibody, which are the locations at which the antibody binds to antigens, i.e., the antigen-binding sites.

Whole antibodies are less than ideal for certain diagnostic and therapeutic uses due to their size, which inhibits distribution to the tissue. In addition, their long half-lives in the body can affect diagnostic sensitivity and cause toxicity. Antibody fragments are preferable to whole antibodies for these uses as they are distributed more rapidly from the blood to tissues than whole antibodies. Antibody fragments may also be preferable to whole antibodies because they are cleared more rapidly from the circulation, i.e., they have a shorter circulating half-life.

Antibody fragments are produced by digesting antibodies using specific enzymes. When an antibody is digested by the enzyme pepsin, the enzyme cleaves the antibody below the "arms" of the "Y," removing the "stem" of the "Y" to generate a $F(ab')_2$ fragment. This is shown in the following figure.

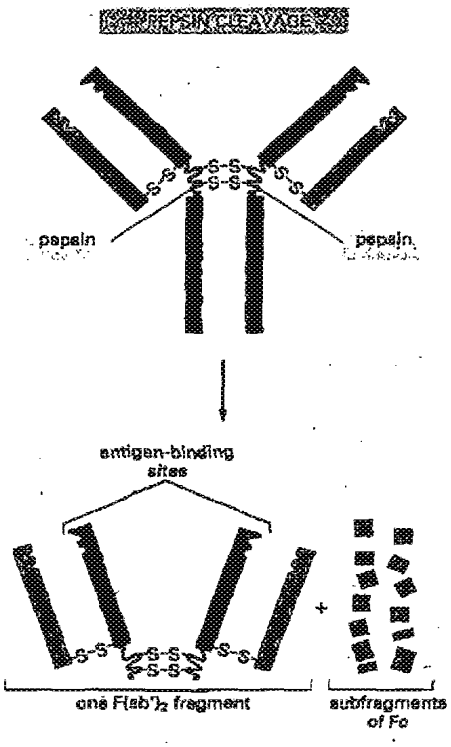

Figure 2.

Appellee's Br. 2-Reverse. A $F(ab')_2$ fragment is comprised of two Fab' fragments, linked at the hinge regions, and is dumbbell-shaped. It is also described as "divalent," because it has two antigen binding sites, one at the end of each arm.[1] A Fab fragment is designated as Fab' when it has at least one cysteine residue in the hinge region of the fragment (see Figure 1 for the hinge region). A Fab' fragment is denoted as Fab'-SH when the cysteine residue(s) have a free thiol (-SH) group.

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[1] A single Fab fragment is "monovalent" because it only has one antigen binding site.

When a $F(ab')_2$ antibody fragment is digested by the enzyme papain, the disulphide bridges between the two "arms" are broken, and two separate Fab' fragments are formed.

Chapman's application is directed to divalent antibody fragments comprising two antibody heavy chains and at least one polymer molecule attached to the heavy chains in a site-specific manner on each chain. Among other things, Chapman teaches combining two separate Fab' fragments (with their light chains removed) using an interchain bridge that contains at least one covalently linked polymer. This interchain bridge indirectly links the sulphur atom of a cysteine residue in one heavy chain to the sulphur atom of a cysteine residue in the other heavy chain via the intervening polymer, rather than having the chains be linked through disulphide bridges. Claim 1, below, is representative; all other claims depend from claim 1.[2]

> 1. A divalent antibody fragment comprising
>
> [a] two antibody heavy chains and
> [b] at least one polymer molecule effective for increasing the circulating half-life of said fragment in covalent linkage,
> [c] each heavy chain being covalently linked to the other by at least one non-disulphide interchain bridge linking the sulphur atom of a cysteine residue in one chain to the sulphur atom of a cysteine residue in the other chain, said cysteine residues being located outside of the variable region domain of each chain, characterised in that the at least one non-disulphide interchain bridge contains the at least one covalently linked polymer molecule.

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[2] The Board noted that claims 2-10, 12, 13, and 15 "fall with claim 1" because separate reasons for their patentability were not provided. Initial Decision, slip op. at 10 (citing 37 C.F.R. § 41.37(c)(1)(vii)). For that reason, only claim 1 is discussed on appeal.

(brackets added). The intervening polymer is characterized as "effective for increasing the circulating half-life" of the antibody fragment. Initial Decision, slip op. at 1-2. Chapman's invention involves joining together two fragments with an interchain bridge containing a polymer, thus achieving a circulating half-life that is intermediate between that of an individual fragment and a whole antibody. Chapman does not dispute the examiner's characterization of Chapman's claimed antibody fragment as being "dumbbell-shaped." See Appellant's Br. 20-23.

U.S. Patent No. 6,025,158 ("Gonzalez") is prior art to Chapman's application. Gonzalez describes linking antibody fragments to a polymer to increase an antibody's circulating half-life for therapeutic purposes. Gonzalez Abstract; id. col.1 ll.13-19; id. col.13 ll.15-24; id. col.15 ll.32-36. Gonzalez notes that the prior art established that a particular polymer, polyethylene glycol ("PEG"), "attached to a sulfhydryl group in the hinge region of a Fab' fragment reduced clearance compared to the parental Fab' molecule." Id. col.1 ll.38-42. Gonzalez discloses, among other things, a single antibody fragment linked to a polymer(s); a "dumbbell-shaped" structure made up of two antibody fragments joined by a polymer; and a "rosette" or other shaped structure composed of more than two antibody fragments joined by a polymer(s). Id. col.35 ll.38-57. Gonzalez also teaches the preparation of antibody fragment-polymer conjugates. It identifies Fab, Fab', Fab'-SH, $F(ab')_2$, scF_v, and F_v as possible choices for the antibody fragment, id. col.21 ll.33-35, and identifies PEG as a potential polymer, id. col.26 ll.39-40. Gonzalez teaches how to attach the polymer to a particular amino acid residue or a particular region; in some embodiments, it teaches doing so without using a disulphide bond.

Gonzalez col.19 ll.35-43. Gonzalez teaches a preference for the cysteine residue as an attachment point. Gonzalez specifically teaches a preference for the cysteine residue in the hinge region of the antibody fragment. See, e.g., id. col.19 ll.62-65. Gonzalez discloses, in its only complete working example, linking PEG to the hinge cysteine of a Fab' heavy chain to make a Fab'-PEG conjugate. Id. cols. 120-23. Like Chapman, Gonzalez discloses that attaching a polymer to an antibody fragment achieves a clearance rate intermediate to that of a whole antibody and that of an individual fragment without an attached polymer. See id. col.1 ll.38-42. U.S. Patent No. 5,436,154 ("Barbanti") is also prior art to Chapman's application. Barbanti describes the use of antibodies for in vivo therapy.

The examiner rejected claims 1-10, 12, 13 and 15 of Chapman's application under 35 U.S.C. § 102(e) as anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as obvious over, Gonzalez. Initial Decision, slip op. at 3. The examiner also rejected claims 1, 13, and 14 under 35 U.S.C. § 103(a) as obvious over Gonzalez and Barbanti. Id. Chapman appealed to the Board.

In analyzing the examiner's rejections, the Board took claims 1, 13 and 14 as representative. Id. The examiner made, and the Board adopted, a number of fact findings ("FFs") concerning the scope of Gonzalez. Relevant for the purposes of this appeal are FFs 3, 7, 8, and 12, which are set out below.

> [FF] 3. The antibody can be a monovalent Fab fragment, a monovalent Fab' fragment which includes one or more cysteine residues in the constant region, or an $F(ab')_2$ antibody fragment which has a hinge cysteine between the Fab' fragments (Gonzalez, at col. 11, ll. 57-66; Ans. 5).

. . . .

[FF]7. Gonzalez also describes conjugates containing a $F(ab')_2$ antibody fragment in which the polymer is attached between the disulphide bridge that would ordinarily link the heavy and lights [sic] chains (Gonzalez, at col. 21, 50-59). In this embodiment, the polymer is attached to a cysteine in the light or heavy chain; the cysteine in the opposite chain is replaced with another amino acid to avoid forming a disulphide bond between the chains (id.).

[FF]8. In another embodiment, Gonzalez describes antibody conjugates in which 'a polymer molecule is used to link together two antibody fragments to form a dumbbell-shaped structure . . . [sic] Such structures can be made by using a polymer molecule derivatized with multiple functional groups permitting the direct attachment, or the attachment by means of bi- or multi-functional linkers, of two or more antibody fragments to the polymer backbone.' (Gonzalez, at col. 35, ll. 45-57; at col. 41, ll. 41-43; see Ans. 5).

. . . .

[FF]12. In regard to the obviousness of the claimed structure, the Examiner states there are explicit teachings of a dumbbell-shaped structure (FF 8) and a Fab' conjugated to PEG in the hinge region via a cysteine residue (FF 6).

Initial Decision, slip op. at 4-6.

The Board reversed the examiner's anticipation rejection over Gonzalez because

> although Gonzalez suggests the antibody structure of claim 1, too much in the way of mental gymnastics would have been necessary for persons of ordinary skill to have 'at once envisage[d]' the claimed antibody structure among the different structures described in the Gonzalez patent . . . . [P]icking and choosing would have been necessary to have arrived at the antibody structure of claim 1.

Id. at 12-13. However, the Board affirmed the examiner's findings and legal conclusion that Chapman's claims 1-10, 12, 13, and 15 would have been obvious over Gonzalez. Id. at 1-10. The Board also affirmed the examiner's rejection of claims 1, 13, and 14 as obvious over Gonzalez in view of Barbanti. Id. at 14-16.

With respect to obviousness over Gonzalez, the Board observed that Gonzalez teaches linking two antibody fragments with a polymer to form a "dumbbell-shaped" structure. Id. at 8-9. The Board also noted that Gonzalez teaches a Fab molecule with a PEG linked to the hinge cysteine of the heavy chain. Id. at 8. The Board then concluded that "the only issue—as recognized by the Examiner—is whether persons of skill in the art would have had reason to join the [Fab'] fragments together using a polymer linked to the hinge cysteine residue." Id. at 8. (citation omitted).

The Board ultimately agreed with the examiner that Gonzalez would have led a skilled artisan to utilize the claimed hinge cysteine because of Gonzalez's preference for linking a polymer there. Id. In particular, the Board observed that Gonzalez refers to prior art that establishes that linking a PEG to the "hinge region of a Fab fragment reduced clearance compared to the parental Fab' molecule . . . ." Id. In addition, the Board emphasized that Gonzalez discloses a complete working example in which a polymer is attached to the hinge cysteine of the heavy chain. Id. at 8-9. Based on these disclosures, the Board found that

> Gonzalez's teaching of the dumbbell-shaped structure, without more guidance in how to make it, together with the disclosure of stable Fab' fragments with a polymer conjugated to a cysteine of the hinge region . . . would have suggested to the ordinary skilled person that such Fab' fragments could be readily linked polymer to polymer using a bifunctional linker, as explicitly stated by Gonzalez when characterizing the dumbbell-shaped antibody structure (FF8).

Id. at 9. By linking the Fab' fragments together at the hinge cysteines using PEG as a linker, a skilled artisan would arrive at Chapman's invention. Id. The Board rejected Chapman's argument that Gonzalez "teaches away" from Chapman's claimed molecule

and also rejected Chapman's argument that the examiner used impermissible hindsight in arriving at Chapman's claimed invention. Id. at 7, 9. With respect to Barbanti, the Board concluded that a person skilled in the art would have had reason to modify Barbanti's claimed antibody fragment with PEG in order to extend its serum half-life (reduce its clearance time) thereby increasing its therapeutic efficacy. Id. at 15. Chapman requested rehearing, and on rehearing, the Board sustained the finding of obviousness. This appeal followed. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(4)(A) and 35 U.S.C. § 141.

DISCUSSION

The Patent and Trademark Office ("PTO") is governed by the Administrative Procedure Act ("APA"), and PTO decisions are reviewed under the APA standard. Dickinson v. Zurko, 527 U.S. 150, 152 (1999). Thus, we review Board's legal conclusions without deference, and review its findings of fact to determine if they are supported by substantial evidence. See Hitzeman v. Rutter, 243 F.3d 1345, 1353-54 (Fed. Cir. 2001); see also 5 U.S.C. § 706(2).

On appeal, Chapman contends that the Board erred as a matter of law in finding representative claims 1, 3, and 14 obvious alone over Gonzalez or in view of Barbanti. Both parties agree that the sole question on appeal is the accuracy of the Board's description of Gonzalez, the primary reference.

Whether an invention would have been obvious is a legal question based on underlying findings of fact, including (1) the scope and content of the prior art; (2) the level of ordinary skill in the prior art; (3) the differences between the claimed invention

and the prior art; and (4) objective evidence of nonobviousness. In re Gartside, 203 F.3d 1305, 1319 (Fed. Cir. 2000) (citing, ultimately, Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966)).

At the outset, Chapman urges that we should reverse the Board's decision finding Chapman's application obvious and conclude that the subject matter of Chapman's invention is non-obvious as a matter of law. Chapman argues that "Gonzalez describes two antibody fragments linked together by polymer molecules to form a dumbbell-shaped structure, but does not specify how and where the antibody molecules are linked by the polymer molecules, or what fragments are to be used." Appellant's Br. 5. To the extent that Chapman argues that there is no motivation to modify Gonzalez to arrive at Chapman's claimed invention, we think that this issue is best addressed in the remand that we order below to correct certain errors in the Board's decision.

Chapman's argument for reversal also rests on his claim that Gonzalez "teaches away" from Chapman's claimed invention as a matter of law. A finding that a reference teaches away can preclude a finding that the reference renders a claim obvious. See DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc., 567 F.3d 1314, 1326 (Fed. Cir. 2009) ("An inference of nonobviousness is especially strong where the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements."). Whether or not a reference teaches away from a claimed invention is a question of fact. See In re Napier, 55 F.3d 610, 613 (Fed. Cir. 1995).

Chapman argues that Gonzalez teaches away from Chapman's claimed invention because Gonzalez teaches the existence of multiple locations on an antibody fragment to which a polymer molecule, or multiple polymer molecules, can be attached. Chapman's apparent theory is that even though Gonzalez shows a preference for attachment at a hinge cysteine residue, the fact that Gonzalez teaches other attachment points "teaches away" from using the hinge cysteine as an attachment point for the polymer. However, Gonzalez specifically discloses a preference for the hinge cysteine as an attachment point for a polymer. See, e.g., Gonzalez, col.19 ll.56-65, col.19 ll.40-46, cols.102-123. Moreover, Gonzalez offers this teaching to solve the very problem that Chapman was trying to solve here—increasing the circulating half-life of the antibody fragment. Id. col.15 ll.15-24. Therefore, Gonzalez does not teach away from using the hinge cysteine as an attachment for a polymer. Further, Chapman argues that while Gonzalez teaches attaching a polymer to a $F(ab')_2$ fragment, Gonzalez does not teach using the polymer as a bridge. While it may be correct that Gonzalez does not explicitly teach using the polymer as a bridge between the two fragments, Gonzalez does not teach away from doing so.

Alternatively, Chapman argues that three of the Board's factual findings concerning the scope and content of Gonzalez are not supported by substantial evidence and that a reversal is required. As discussed below, the government agrees that the Board's opinion includes three erroneous statements, but the government urges that the three errors in the Board's opinion are harmless. The judicial review provision of the APA includes a harmless error rule. See 5 U.S.C. § 706 ("[D]ue account shall be

taken of the rule of prejudicial error"). We have noted that "the harmless error rule applies to appeals from the Board just as it does in cases originating from district courts." In re Watts, 354 F.3d 1362, 1369 (Fed. Cir. 2004) (citing In re McDaniel, 293 F.3d 1379, 1385-86 (Fed. Cir. 2002); Gechter v. Davidson, 116 F.3d 1454, 1457 (Fed. Cir. 1997)). We have said that

> to prevail the appellant must not only show the existence of error, but also show that the error was in fact harmful because it affected the decision below. See Munoz v. Strahm Farms, Inc., 69 F.3d 501, 504 (Fed. Cir. 1995) ("The correction of an error must yield a different result in order for that error to have been harmful and thus prejudice a substantial right of a party."); see also Palmer v. Hoffman, 318 U.S. 109, 116 (1943) ("He who seeks to have a judgment set aside because of an erroneous ruling carries the burden of showing that prejudice resulted.").

Id. The Supreme Court has recently reaffirmed that "review of ordinary administrative proceedings" is like "review of civil cases in this respect. Consequently, it is clear that the burden of showing that the error is harmful normally falls upon the party attacking the agency's determination." Shinseki v. Sanders, 129 S. Ct. 1696, 1706 (2009) (citations omitted). In the light of this standard, we proceed to consider the three errors, and whether they were harmless.

First, Chapman takes issue with the Board's statement that "the Examiner finds Gonzalez teaches a dumbbell-shaped antibody structure comprised of two monovalent Fab' fragments (FF 8, 12) and describes linking them via a polymer molecule." Initial Decision, slip op. at 7. On appeal, the government agrees that Gonzalez does not teach linking "two monovalent Fab' fragments . . . via a polymer." Indeed, the examiner's fact findings 8 and 12, relied on by the Board, do not suggest otherwise, as

the government concedes. See Oral Arg. at 18:07-18:19 ("I think that in the first instance, they conflate two correct fact findings, and the way they conflate them is not correct, so that sentence is in error, but the two fact findings are not in error . . . ."). The government contends that this error is harmless as the Board did not base its obviousness rejection on this particular statement but was simply (erroneously) describing a position taken by the examiner. We agree with the government that that Board's decision on rehearing makes clear that the Board is not relying on any such explicit disclosures in Gonzalez.

As to the second alleged error, the Board stated that "Gonzalez describes a divalent antibody in which the polymer is linked between light and heavy chains and only one cysteine residue is present." Initial Decision, slip op. at 8 (citing FF 7; Appellant's Br. 6) (emphasis added). Citing column 21, lines 50-59 of Gonzalez, the examiner's FF 7 states that Gonzalez describes conjugates containing an "$F(ab')_2$ antibody fragment in which the polymer is attached between the disulphide bridge that would ordinarily link the light and heavy chains." Id. at 4 (emphasis added). Chapman argues that both the examiner and the Board misunderstand the relevant disclosure in Gonzalez, which reads as follows:

> In yet another preferred embodiment, the conjugate contains a $F(ab')_2$ antibody fragment attached to no more than about 2 polymer molecules, wherein every polymer molecule is attached to a cysteine residue in the light or heavy chain of the antibody fragment that would ordinarily form the disulfide bridge linking the light and heavy chains, wherein the disulfide bridge is avoided by substituting another amino acid, such a serine, for the corresponding cysteine residue in the opposite chain.

Gonzalez, col.21 ll.51-59. Chapman argues that the examiner and the Board misinterpreted this passage and that in this embodiment, the polymer is not serving as a link between the light and heavy chain; it is attached to either the light or the heavy chain. The government conceded at oral argument that Chapman's reading of this passage is correct. See Oral Arg. at 24:40-24:47 ("[I]n Gonzalez . . . the polymer is attached to either the light or the heavy chain; it's not linking the light and heavy chains.").

The third alleged error concerns FF 3, wherein the Board stated that "[t]he antibody can be a monovalent Fab fragment, a monovalent Fab' fragment which includes one or more cysteine residues in the constant region, or an $F(ab')_2$ antibody fragment which has a hinge cysteine between the Fab' fragments." Initial Decision, slip op. at 4 (citing Gonzalez col.11 ll.57-66; Answer 5). However, it is clear that, as the government concedes, Gonzalez teaches six different possible antibody fragments: F(ab), F(ab'), F(ab')-SH, $F(ab')_2$, scF_v, and F_v. Gonzalez, col.21 ll.33-41; Oral Arg. at 27:58-28:00 ("There are more than three [antibody fragments] disclosed [in Gonzalez]."). FF 3 is incorrect as both parties agree that Gonzalez discloses more than three choices for an antibody fragment.[3]

The government argues that these errors are harmless, but we conclude that these errors are harmful because they increase the likelihood that Chapman was

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[3] Chapman points out that the Board's rehearing decision can be read even more restrictively, i.e., to suggest that in Gonzalez, only the Fab' fragments and not even the Fab or $F(ab')_2$ fragments can be formed into a dumbbell-shaped structure. See Final Decision, slip op. at 4.

erroneously denied a patent on grounds of obviousness. If the Board based its decision on a misunderstanding of Gonzalez, its conclusions regarding obviousness are called into question. With respect to the second error, the Board was mistaken as to whether Gonzalez teaches the use of a polymer to link the light and heavy chains in a $F(ab')_2$ fragment in the cited embodiment. Therefore, Chapman's use of a polymer to link together two F(ab') fragments may be less likely to be obvious. Further, as to the third error, if the Board did not appreciate the full scope of antibody fragments disclosed in Gonzalez, we cannot be confident about its ultimate conclusion that the selection of one of them to form Chapman's molecule is obvious, as it appears that there are more possibilities from which to choose. Because we cannot say with confidence that the Board would have reached the same conclusion in the absence of these errors, we are persuaded they are indeed harmful. See Kotteakos v. United States, 328 U.S. 750, 765 (1946) ("[I]f one cannot say, with fair assurance, . . . that the judgment was not substantially swayed by the error, it is impossible to conclude that substantial rights were not affected." This is not a situation where "an agency's path, though convoluted, can be discerned." In re Huston, 308 F.3d 1267, 1281 (Fed. Cir. 2002) (quotation and citation omitted).

On remand, the Board need only revisit its conclusion of obviousness in light of a corrected understanding of Gonzalez. The Board is in no way precluded from, and indeed may be correct in, finding the claims to be obvious, particularly in the light of Gonzalez's disclosure of joining two antibody fragments together with a polymer to make a dumbbell-shaped structure.

VACATED and REMANDED

COSTS

No costs.